PAPER

Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis at autopsy

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Background: Variable compliance with antiepileptic drugs (AEDs) is a potentially preventable cause of sudden unexplained death in epilepsy (SUDEP). Hair AED concentrations provide a retrospective insight into AED intake variability.
Methods: We compared hair AED concentration variability in patients with SUDEP (n = 16), non-SUDEP epilepsy related deaths (n = 9), epilepsy outpatients (n = 31), and epilepsy inpatients (n = 38). AED concentrations were measured in 1 cm hair segments using high performance liquid chromatography. Individual patient hair AED concentration profiles were corrected for ''washout'' using linear regression analysis. The coefficient of variation (CV) of the corrected mean hair AED concentration provided an index of variability of an individual's AED taking behaviour. Hair sample numbers varied between subjects, and so weighted regression estimates of the CV were derived for each group.
Results: The CV regression estimates for each group were: SUDEP 20.5% (standard error 1.9), non-SUDEP 15.0% (3.9), outpatients 9.6% (1.4), and inpatients 6.2% (2.7). The SUDEP group therefore showed greater hair AED concentration variability than either the outpatient or the inpatient groups ($p<0.0001$).
Conclusion: Observed variability of hair AED concentrations, reflecting variable AED ingestion over time, is greater in patients dying from SUDEP than in either epilepsy outpatients or inpatients. SUDEP, at least in a proportion of cases, appears preventable.

Sudden unexplained death in epilepsy (SUDEP) is an important cause of epilepsy related death,[1] with an annual incidence among patients with epilepsy of 1–2 per 1000.[2] More frequent or more severe seizures increase the risk.[3] Better seizure control by medication ought to reduce the likelihood of SUDEP, yet surprisingly there is no evidence for this.[4] Antiepileptic drug (AED) taking behaviour inferred after death from third party histories is unreliable. Postmortem AED blood levels are difficult to interpret due to drug redistribution.[5]

Drugs taken either therapeutically or recreationally incorporate into hair and remain relatively stable.[6] Hair grows at ~1 cm per month[7]; observed variability in segmental hair AED concentrations therefore offers a retrospective insight into drug taking behaviour.

METHODS

We hypothesised that SUDEP patients have more variable AED ingestion than outpatient controls, and that this would be reflected in greater variability in intersegmental hair AED concentrations.

All patients with epilepsy undergoing coroner's autopsy at the University Hospital of Wales, Cardiff, UK, and at the Royal Preston Hospital, Lancashire, UK, and brought to our attention between January 1998 and March 2002, were considered for the study. Those prescribed phenytoin, carbamazepine, phenobarbitone, or lamotrigine (monotherapy or polytherapy) were eligible. Patients on valproic acid monotherapy were excluded, as there was no reliable hair analysis assay at the time. Autopsy reports and case records were hand searched. SUDEP was defined using standard criteria.[2] All cases designated either definite or probable SUDEP were included as SUDEP. Hair samples were also available from 31 epilepsy outpatients attending the Cardiff Epilepsy Unit, and 38 epilepsy inpatients resident in the Chalfont Centre, London, whose regular medication ingestion was assured.[8]

Ethical approval was obtained from local ethics committees. Hair AED analysis results were made available to the pathologist and coroner. A sample of 15–20 hairs (20 mg) cut close to the posterior vertex scalp, was divided into 1 cm segments, weighed, and then digested in 1.5 M sodium hydroxide for 2 h at 40°C.

AED concentrations were measured using high performance liquid chromatography.[9] The decline in hair AED concentration along the proximal-distal axis (''washout effect''[10]) was corrected using linear regression analysis as previously described.[11] Each patient's corrected mean, standard deviation (SD), and coefficient of variation (CV) of hair AED concentration were calculated.

The CV of each individual's hair AED concentration was used to infer variability in AED taking behaviour.[8 11] However, hair sample numbers (depending on hair length) varied between three and ten, and more weight should be given to a CV based upon ten samples than upon three. We therefore fitted a weighted linear regression model of the SD on the mean, passing through the origin, basing the weights upon the sample number. The regression coefficient was then an estimate of the CV, and gave greater weighting to patients with larger numbers of samples. Patients with hair AED levels of zero could then be included, although not influencing the analysis. Such models were fitted to the four groups (SUDEP, non-SUDEP, outpatients, and inpatients) and the regression estimates of the CV compared by combining the estimated standard errors. Residual checks were made to ensure that the model was appropriate.

Abbreviations: AED, antiepileptic drug; CV, coefficient of variation; SD, standard deviation; SUDEP, sudden unexplained death in epilepsy

RESULTS

A total of 30 patients underwent hair sampling at autopsy. Available clinical information was often limited and a definite epilepsy diagnosis and cause of death could be established in only 25 cases (83%). Sixteen of these met the criteria for probable or definite SUDEP (37.5% female; mean group age 43.3±16.6 (range 10–70) years) and nine were designated as non-SUDEP (33.4% female; mean group age 48.3±24.7 (range 16–79) years). Hair AED data were also available from a previous study of 31 epilepsy outpatients (41% female; mean group age 32.7±7.31 (range 19–47) years) and from a previously published series of 38 epilepsy inpatients.[8] Clinical details of the SUDEP and non-SUDEP groups are given in table 1. Regression estimates of the CV for each group were: SUDEP 20.5% (standard error 1.9); non-SUDEP 15.0% (3.9), outpatients 9.6% (1.4), inpatients 6.2% (2.7). The SUDEP group therefore showed significantly greater variability in hair AED concentrations than either outpatients or inpatients ($p<0.0001$). Inpatients showed significantly less variability in AED hair concentration than outpatients ($p = 0.027$). Figure 1 illustrates the regression lines whose slopes are the estimates of the CV for each group.

Patient 3 was pregnant and died from SUDEP at 36 weeks gestation; a 30 weeks gestation hair sample had previously been taken. The similar mean hair AED concentrations antenatally (38.5±6.1 ng/mg; CV = 15.9%) and at autopsy (32.9±5.4 ng/mg; CV = 16.4%) indicate that postmortem hair samples are directly comparable to samples taken in life.

Two SUDEP cases (patients 7 and 8) showed no detectable hair AEDs. In patient 7, phenytoin was completely absent from all ten hair segments analysed, suggesting total AED non-compliance over >10 months before death. This patient is therefore at the point (0,0) through which the line is forced to pass, and so did not contribute to the regression. In patient 8, lamotrigine had been prescribed at a low dose only briefly before death; her hair data were therefore excluded.

DISCUSSION

This is the first use of hair analysis to explore AED drug taking behaviour in patients following SUDEP. Observed variability of segmental hair AED concentrations was significantly greater among SUDEP patients compared to epilepsy outpatients or inpatients. Since observed variability of segmental hair AED concentrations reflects drug intake variability over time, our data suggest that variable drug taking behaviour is associated with SUDEP.

Previous studies of AED taking behaviour in epilepsy related death gave conflicting results. The retrospective study of Tennis *et al*[12] suggested erratic compliance was a causative factor. Nilsson *et al*[13] demonstrated that patients undergoing regular blood therapeutic drug monitoring were at half the risk of SUDEP compared to non-monitored patients; however, their observed variability of blood AED levels was similar, and so there was no definite evidence of non-compliance amongst SUDEP patients. Opeskin *et al*[14] found postmortem blood AED concentrations were equally likely to be undetectable, subtherapeutic, or therapeutic following SUDEP or non-SUDEP death, and concluded that AED compliance was relatively unimportant in SUDEP. However, postmortem AED levels are unreliable owing to postmortem drug redistribution,[5] and hence autopsy blood levels do not necessarily reflect compliance.

Our study offers a meaningful insight into AED drug taking behaviour in SUDEP using a technique that provides retrospective information over time, while still allowing direct comparison of samples obtained both during life and following death.

The low regression estimate of CV in the highly supervised inpatient group supports the validity of hair AED concentration variability as an index of AED compliance.

Furthermore, the similarity of hair AED data derived from samples taken before and after death (patient 3) supports the reliability of postmortem hair analysis. However, hair AED analysis has certain limitations. First, it relies upon observed

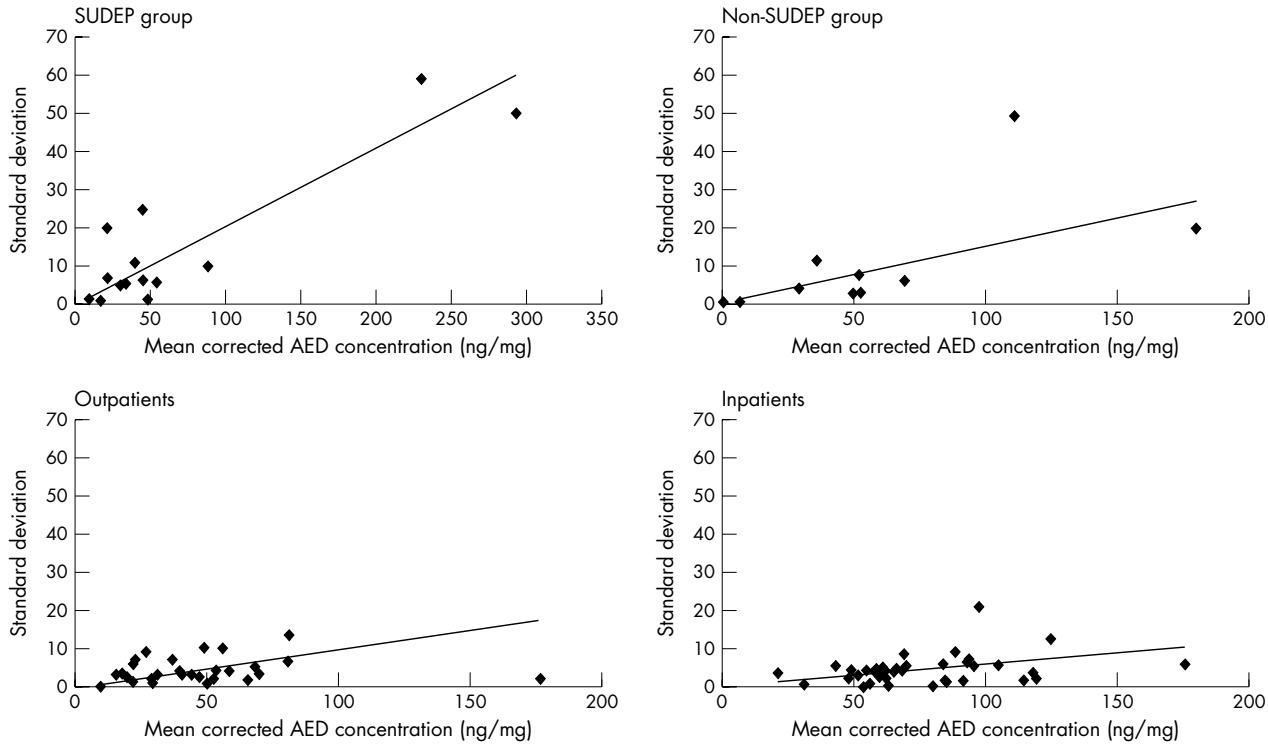

Figure 1 Weighted regression plots for each of the four groups: SUDEP group, non-SUDEP group, outpatients, and inpatients.

Table 1 Clinical details of the SUDEP and non-SUDEP groups

Patient	Sex	Age (years)	Cause of death	Epilepsy type	Main seizure type(s)	AED 1 (mg/day)	AED 2 (mg/day)
1	F	10	SUDEP	Unclassified	GTCS	Lamotrigine (100)	Valproic acid
2	M	24	SUDEP	Unclassified	Unknown	Phenytoin (200)	
3	F	25	SUDEP	Juvenile myoclonic	GTCS	Lamotrigine (250)	
4	F	32	SUDEP	Juvenile myoclonic	GTCS	Lamotrigine (150)	
5	M	32	SUDEP	Localisation related (neurofibromatosis 1)	CPS and GTCS	Carbamazepine (200)	
6	F	36	SUDEP	Unclassified	GTCS	Carbamazepine (400)	
7	F	36	SUDEP	Unknown	GTCS	Phenytoin (500)	Gabapentin (2000)
8	F	42	SUDEP	Probable localisation related	CPS and GTCS	Lamotrigine (25)	Ethosuximide (500), valproic acid (1500)
9	F	51	SUDEP	Localisation related	CPS and GTCS	Phenytoin (200)	Gabapentin (1200)
10	F	51	SUDEP	Unknown	Unknown	Carbamazepine (200)	Phenobarbitone (60)
11	M	52	SUDEP	Localisation related (cavernoma)	GTCS	Carbamazepine (1000)	
12	F	52	SUDEP	Probable SLRE	SPS and GTCS	Carbamazepine (1000)	
13	M	55	SUDEP	Localisation related (cortical dysplasia)	CPS	Carbamazepine (1000)	Lamotrigine (300)
14	M	57	SUDEP	Localisation related (extradural haematoma)	CPS and GTCS	Phenytoin (300)	Valproic acid (2000)
15	F	68	SUDEP	Juvenile myoclonic	GTCS	Phenytoin (300)	Phenobarbitone (180)
16	M	70	SUDEP	Localisation related	Unknown	Phenytoin (200)	Valproic acid (1000)
17	M	18	Status epilepticus	Probable localisation related	GTCS	Lamotrigine (600)	Clobazam (30)
18	F	36	Status epilepticus	Idiopathic generalised	GTCS/atypical absences	Lamotrigine (400)	Clobazam (10)
19	M	64	Alcohol related	Localisation related	GTCS	Carbamazepine (200)	
20	M	30	Closed head injury	Unclassified	Unknown	Phenobarbitone	
21	M	47	Myocardial infarction	Unclassified	GCTS	Phenytoin (400)	
22	F	78	Myocardial infarction	Unclassified	Unknown	Lamotrigine (100)	
23	M	67	Ischaemic heart disease	Unclassified	Unknown	Carbamazepine	
24	M	16	Drowned in bath	Localisation related (astrocytoma)	CPS and GTCS	Lamotrigine	Phenytoin
25	M	79	Ischaemic heart disease	Localisation related (stroke)	GTCS	Phenytoin (200)	

CPS, complex partial seizures; GTCS, generalised tonic-clonic seizures; SLRE, symptomatic localisation related epilepsy; SPS, simple partial seizures.

AED concentration variability and so cannot distinguish prescribed changes from compliance changes, or identify consistent non-compliance over time. Secondly, it does not provide information on drug taking behaviour immediately before death, since it takes about 5 days for drug sequestrated into the follicle to appear at the scalp; therefore short term non-compliance immediately before death may have been overlooked. This limitation applies also to therapeutic drug monitoring studies,[13] since AED levels were measured at variable times before death. Thirdly, hair AED concentrations or rate of hair growth may be influenced by other medications or illness, but this effect is likely to be small. Finally, one SUDEP patient with no detectable hair AED almost certainly had not taken her prescribed AED, yet with zero hair AED concentration, there was zero hair AED variability. Her slope in the weighted regression analysis passed through zero and so did not influence the overall group slope. Nevertheless, even having effectively excluded this patient, our data demonstrate a significant difference in hair AED concentration variability between the SUDEP and epilepsy outpatients.

Patients taking valproic acid monotherapy were excluded, as no hair valproate assay was available; thus idiopathic generalised epilepsies were under-represented in this study. Idiopathic epilepsies generally are more medication responsive than symptomatic (or cryptogenic) epilepsies; thus acceptable AED drug taking behaviour may be more important for idiopathic than symptomatic epilepsies in maintaining seizure freedom. Furthermore, idiopathic generalised epilepsy patients may be more vulnerable to SUDEP than those with localisation related epilepsies.[15] Excluding patients taking valproate may therefore have underestimated the relationship between variable drug taking behaviour and SUDEP.

SUDEP in pregnancy (patient 3) raises particular concerns. Epilepsy is the second commonest cause of maternal death in the UK.[16] Women frequently discontinue prescribed medication in pregnancy without consulting their physician.[11] Serum AED levels also fall from physiological changes in pregnancy.[17] The hair analyses of patient 3 during pregnancy and following death suggest reasonably consistent AED tissue levels over the preceding months. Thus, despite our overall conclusion, this case fails to reassure that good medication concordance necessarily prevents SUDEP as a cause of maternal death.

In summary, our data indicate that observed variability of segmental hair AED concentrations is significantly greater in SUDEP patients compared to epilepsy outpatients or inpatients. The most likely explanation is that SUDEP patients have greater variability in taking AED medication. We therefore conclude that SUDEP, at least in some cases, is preventable. Emphasising concordance with AED medication in patients with epilepsy appears essential.

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REFERENCES

1 **Nashef L**. Sudden unexpected death in epilepsy: terminology and definitions. *Epilepsia* 1997;**38**(suppl 11):S6–8.
2 **Annegers JF**. Sudden unexpected death in epilepsy: United States perspective on definitions and classifications. *Epilepsia*, 1997;**38**(suppl 11);S9–12..
3 **Dasheiff RM**. Sudden unexplained death in epilepsy: a series from an epilepsy surgery programme and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 1991;**8**:216–22.
4 **Walczak TS**, Leppik IE, D'Amelio M, *et al*. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001;**56**:519–25.
5 **Tomson T**, Skold A-C, Holingren P, *et al*. Post mortem changes in blood concentration of phenytoin and carbamazepine: an experimental study. *Ther Drug Monit* 1998;**20**:309–12.
6 **Uematsu T**. Utilisation of hair analysis for therapeutic drug monitoring. *Forensic Sci Int* 1993;**63**:201–8.
7 **Saitoh MM**, Uzuka RL, eds. *Advances in biology of skin*, Vol 9. Oxford: Pergamon Press, 1969:183–202.
8 **Williams J**, Patsalos PN, Mei Z, *et al*. Relation between dosage of carbamazepine and concentration in hair and plasma samples from a compliant in-patient epileptic population. *Ther Drug Monit* 2001;**23**:15–20.
9 **Saris LA**, Brekelmans GFT, van der Linden GJ, *et al*. High performance liquid chromatography of carbamazepine metabolites in human hair. *J Chromatogr B* 1997;**691**:409–15.
10 **Mei Z**, Williams J. Simultaneous measurement of phenytoin and carbamazepine in human hair by high performance liquid chromatography. *Ther Drug Monit* 1997;**19**:92–4.
11 **Williams J**, Myson V, Steward S, *et al*. Self-discontinuation of antiepileptic medication in pregnancy: detection by hair analysis. *Epilepsia* 2002;**44**:824–31.
12 **Tennis P**, Cole TB, Annegers JF, *et al*. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. *Epilepsia* 1995;**36**:29–36.
13 **Nilsson L**, Bergman U, Diwan V, *et al*. Antiepileptic drug therapy and its management in sudden unexplained death in epilepsy: a case control study. *Epilepsia* 2001;**42**:667–3.
14 **Opeskin K**, Burke MP, Cordner SM, *et al*. Comparison of antiepileptic drug levels in sudden unexpected deaths in epilepsy with deaths from other causes. *Epilepsia* 1999;**40**:1795–8.
15 **Nilsson L**, Farahmand BY, Persson P-G, *et al*. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999;**353**:888–93.
16 **UK Department of Health**. *Why mothers die 1997–1999. Confidential enquiries into maternal deaths 2001*. Dorchester: RCOG Press, 2001, Available at:http://www.cemach.org.uk/publications.htm (accessed 3rd October 2005).
17 **de Haan G-J**, Edelbroek P, Segers J, *et al*. Gestation-induced changes in lamotrigine pharmacokinetics: a monotherapy study. *Neurology* 2004;**63**:571–3.